Jan. 20, 2016

Study unravels link between surgery, diabetes remission

By Krishna Ramanujan

Researchers and doctors have known for years that patients who receive bariatric surgeries – gut surgeries with the goal of weight loss – often experience remission of Type 2 diabetes. Clinicians find that diabetes remission begins within days after such surgeries, well before weight loss occurs.

No one has fully understood the mechanisms behind these effects, but a recent Cornell-led study published in the journal Gut provides clues to the mystery. The findings open doors for novel drug treatments to treat Type 2 diabetes.

The study, which was done with mice, reveals that bariatric surgeries increase bile acid concentrations, and in concert with a bile acid receptor called TGR5, play critical roles in balancing glucose levels in the body, which help treat diabetes. Signaling from TGR5 was found to regulate several metabolic outcomes, including: glucose homeostasis, inflammation and liver insulin signaling.

But the researchers caution that bariatric surgery may not be the answer for all patients suffering from Type 2 diabetes.

"In the United States, bariatric surgeries are primarily allowed for obesity treatment, generally requiring a BMI over 40 or a BMI over 35 with significant obesity-related co-morbidities," though some clinicians argue for expanding the use of these surgeries for treatment of diabetes, said Bethany Cummings, assistant professor of biomedical sciences in Cornell's College of Veterinary Medicine and the paper's senior author. Anne McGavigan, a postdoctoral researcher in Cummings' lab, is the paper's first author.

"Our goal is to study these surgeries in order to identify novel therapeutic targets, because surgery is not without risks and a drug is much easier to widely distribute amongst patients," said Cummings. The study points to TGR5 as a possible target for diabetes treatment, and more research on this bile acid receptor may also lead to treatments that exploit TGR5 and bile acid links, she added.

In the study, the researchers conducted a sham surgery or a common bariatric surgery called a vertical sleeve gastrectomy (VSG) in high-fat-fed normal lab mice, and in specially engineered mice without TGR5 receptors.

In a VSG, surgeons cut along the curve of the stomach and remove roughly 70 percent, leaving a tubular organ. The sham surgery created sutures in the stomach but didn't remove any stomach tissue, to test if surgery itself contributed to effects. A third group of normal mice were given a sham surgery but were also placed on a restricted diet to control for weight loss.

Cummings and colleagues found that after the VSG, circulating concentrations of bile acids in the normal mice greatly increased – for reasons not yet understood. Furthermore, VSG in the normal mice favored beneficial bile acids. Bile acids come in different forms, a less beneficial hydrophobic (water repelling) form and a healthier hydrophilic (water attracting) form. The experiments revealed that signaling from TGR5 specifically contributed to the increase in

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hydrophilic bile acids, which in turn helped balance and regulate glucose in these mice after VSG surgery.

While weight loss does contribute to Type 2 diabetes remission, “the thing we are excited about is it’s not just the weight loss,” said Cummings. “Coming up with methodologies other than weight loss to treat diabetes is critical.”

Future work will further explore TGR5 function, as there appears to be a lot that we still don’t know about the function of this receptor, Cummings said.

“Doing these surgeries in tiny mice is no small feat, but it helps move our understanding of how bariatric surgery causes Type 2 diabetes remission forward,” she added.

Co-authors include researchers from the University of California, Davis, and Lilly Research Labs.

The study was funded by Eli Lilly and Co., the National Institutes of Health and Cornell University.